Efficacy and safety of colchicine in inflammatory skin diseases: a retrospective, monocentric study in a large tertiary center

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Abstract: Introduction: Colchicine is an ancient, but rarely used drug. Little data exist on its efficacy and safety in patients suffering from skin diseases. The objective of our study was to determine whether colchicine showed favorable efficacy and safety in our patients during the last 20 years.Methods: The hospital database was searched for patients treated with colchicine in the last 20 years (January 1, 1998 to December 31, 2017). Overall, total of 41 patients were included in our study.Results: In 63.4% of all patients, either a complete response or an improvement of disease was observed. Adverse events occurred rarely.Discussion: Colchicine is an effective and safe treatment.

DOI: https://doi.org/10.1080/09546634.2019.1690621

Efficacy and safety of Colchicine in inflammatory skin diseases: a retrospective, monocentric study in a large tertiary center

Short title: Colchicine – safe and effective

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Word count: 1526

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Abstract

Introduction:

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Methods:

The hospital database was searched for patients treated with colchicine

in the last 20 years (January 1, 1998 to December 31, 2017). Overall, total of 41 patients were included in our study.

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In 63.4% of all patients, either a complete response or an improvement of disease was observed. Adverse events occurred rarely.

Disscussion:

Colchicine is an effective and safe treatment.

Keywords: Colchcine, Kolchizin, inflammatory dermatoses, neutrophils, neutrophilic dermatoses

Introduction

Colchicine is one of the oldest drugs that is currently used in dermatology. The first documented use goes back to 1500 BC, where dapsone has was used for joint swelling in Egypt.[1] The first official report of successful treatment of gout with colchicine was published by Baron Anton von Storck in 1793.[2]

It is extracted from the herbaceous plant Colchicum autumale.[3] While colchicine appears initially as pale yellow, after UV- exposure, a conversion to different photoisomers takes place and the substance darkens.[3] After one hour plasma concentrations are reached and after 10 hours half of the concentration is metabolized by the liver.[4, 5] It interacts with the CYP3A4 enzyme and can therefore change the bioavailability of other drugs as macrolides, cyclosporine or ketoconazol.[6]

Colchicine exhibits its anti-inflammatory properties through numerous mechanisms of action. Colchicine interferes with the formation of microtubules and increases intracellular cyclic adenosine monophosphate causing suppression of leukocyte function.[7] Colchicine impairs chemotaxis, migration and phagocytic capability of neutrophils,[8, 9] and inhibits DNA synthesis.[10, 11] Also degranulation of mast cells can be interrupted.[12]

The use of colchicine is established for the treatment of gout,[13] atrial fibrillation,[14] pericarditis,[15, 16] familial Mediterranean fever,[17] posttransplant capillary leak syndrome and renal failure.[18] Possible protective benefits in stroke/TIA,[19] atherosclerotic cardiovascular disease,[20, 21] and periodontal tissue destruction[22] have been described.

Additionally, this traditional drug has been reported to be beneficial in numerous other diseases, such as amyloidosis,[23] Wells' Syndrome,[24] Schamberg's disease,[25] junctional epidermolysis bullosa,[26] epidermolysis bullosa acquisita,[27] Hidradenitis suppurativa,[28] lichen planus pigmentosus,[29] aphthous stomatitis (apthosis), Behcets syndrome,[30]

condylomata acuminate (as topical solution), palmoplantar pustulosis, psoriasis, scleroderma, urticarial vasculitis as well as sweet syndrome,[3] polychondritis.[31]

In a review of Robinson et al. the most common indications and their evidence were analyzed (Table 1).[32]

In our department, we administered colchicine for 3 main indications: leucocytoclastic (small vessel) vasculitis, Behcet's disease and recurrent benign aphthosis.

Vasculitis has been an indication for colchicine for a long time. In a case series, 9 of 13 participants (69.2%) with leucocytoclastic vasculitis achieved disease control.[33] In a report of 6 patients with necrotizing vasculitis, 5 patients showed clinical improvement.[34] In a retrospective study (n=57).[35] Yet, the only prospective, randomized controlled trial (n= 20) could not yet prove significant therapeutic effect of colchicine.[36]

In a prospective, open, cross-over trial with 20 patients with recurrent aphthous stomatitis (aphthosis), 19 patients showed improvement under 0.5mg colchicine three times daily.[37] A case series with 3 patients reported similar efficacy.[38]

For Behcet's disase a double-blind, randomized, placebo-controlled trial (n=116) showed a high efficacy of colchicine in this disease.[39] Several other studies came to similar results.[40-42]

Besides its efficacy, several side effects have been described. Even though colchicine is generally well tolerated, gastrointestinal toxicity, including diarrhea, nausea and vomiting can occur after intake.[3, 43] Hepatotoxicity has been described, especially when concomitant intake of other medications that interact with CYP3A4, i.e. macrolides, has taken place.[44] Feared complications included anemia, neutropenia, rhabdomyolysis[45] as well as neuromyopathy.[46] Overdoses can be potentially lethal.[47]

With focus on young patients, azoospermia[48] as well as infertility[49] have been associated with colchicine intake. Yet even though cytogenetic effects have been shown in animals, there is no data that suggests an increased risk of birth defects[49-51]. A single case of trisomy 21 after parental use has been reported [52]

The objective of our study was to determine whether colchicine showed favorable efficacy and safety in our patients during the last 20 years.

Methods

Data acquisition

Permission was granted by the cantonal ethic commission (BASEC-Nr. ID 2018-00854). Using the hospital data base, a search for patients that were treated with Colchicine at the Department of Dermatology at the University Hospital Zurich in the last 20 years (01.01.1998-31.12.2017) was performed. 67 patients matched these criteria. 2 were younger than 18 years and had to be excluded, 20 patients did not have follow-up visits. In 4 cases the data set required for analysis was incomplete (Figure 1). Overall, data from 41 patients were analyzed.

The primary objective was to evaluate treatment efficacy- as judged by the physician. Treatment response was categorized into 4 groups (complete response, improvement of disease, stable disease and progression of disease). In the majority of cases treatment response was measured after 3 months. However, if colchicine intake was terminated sooner despite treatment success, treatment response was considered as success (either complete response or improvement of disease). The secondary objective was to evaluate adverse events described during treatment with colchicine. Other parameters as age, gender, diagnosis, dosage, duration of intake, and previous treatments were analyzed.

Statistical analysis

The D'Agostino & Pearson omnibus normality test, the Shapiro-Wilk normality test, and the Kolmogorov-Smirnov test (with Dallal-Wilkinson-Lilliefor p value) were used to for normality testing. For statistical analysis the Kruskal-Wallis-Test or, if appropriate, the Mann Whitney U test were performed.

Results

41 patients were included in our study. 17 were male, 24 female. The average age was 50±18 years, the youngest was 18 years, the oldest 88 years. Previous systemic treatments included most of the time dapsone (n=11) and systemic steroids (n=9). 4 patients had colchicine previously but stopped due to various reasons. The target dose was in most cases 1 mg (n=26), 12 patients received 1.5 mg and only 3 patients had a dosage of 2 mg.In most cases, colchicine was either first- or second line treatment. In 19 cases systemic steroids were used concomitantly (Table 2). 15 patients were treated with colchicine for aphthosis, 11 patients for vasculitis, and 7 for Behcet's disease. Other diagnoses included lupus erythematodes, sweet syndrome, gout, hypereosinophilic dermatitis, rosacea, Well's syndrome, and urticarial (Table 2, Figure 2A).

In 6 out of 15 patients with from aphthosis an improvement was seen. 2 had a complete response and in 4 a stable disease was observed. A progression of disease was found in 3 patients. In patients suffering from small vessel vasculitis (IgA positive and IgA negative) overall 7 patients showed a treatment response to colchicine, while only 4 had a stable disease or progression of disease. Complete responses were also seen in patients with rosacea (n=1), gout (n=1) and sweet syndrome (n=1) (Table 3, Figure 2B).

Overall, 8 patients (19.5%) had a complete response, 18 (43.9%) showed an improvement, 11 (26.8%) had stable disease and in 4 cases (9.8%) a progression of disease was found (Figure 2C).

The most common adverse events included diarrhea (n=6, 13.3%), nausea (n=4, 8.9%) and vomiting (n=2, 4.4%). All other side effects were only seen in less than 5% of all patients and included, alopecia, an allergic type I reaction (not otherwise specified), stomatitis, visual

deficiency, pregnancy, peripheral neuropathy, myopathy/rhabdomylosis, headache, vaginal bleeding, arthralgia, vertigo and pruritus (Table 4).

Increased liver enzymes were seen in 8 patients (27.6%), which had normal transaminases before initiation of colchicine treatment. Kidney function became pathological in 5 patients (11.1%). There were no abnormal thyroid parameters observed. Also no patient yielded increased cholesterol or triglycerides (Table 4).

The reasons for termination of therapy included adverse events in 2 cases, success of therapy with complete response in 14 cases. 10 patients stopped taking colchicine due to failure of treatment. 2 patients had other reasons. In 10 patients no reasons was disclosed or documented. 3 patients were still on treatment during our analysis. (Table 3).

Discussion

The objective of our study was to determine whether colchicine showed favorable efficacy and safety in our patients during the last 20 years. In this analysis, we found that in 63.4% of all patients, either a complete response or improvement of disease was observed. Colchicine was effective in patients with aphthosis, small vessel vasculitis and Behcet's disease. The number of patients in other diseases was too small to draw any conclusions. It remains unclear what feature distinguished patients who showed a non-favorable treatment response (stable disease or progression of disease). Possibly, bad adherence might account for failure of treatment in some patients, but this remains speculative. Our results are in line with several previous studies that showed a high efficacy, especially among patients with aphthosis and Behcet's disease. Also in vasculitis our data support the majority of positive reports and are in contrast to the only randomized, controlled, double-blind trial that did not find efficacy of colchicine.[36]

Our study has several limitations, including the retrospective, monocentric design. No correlation of weight and dosage was performed, as weight was seldom documented.

In contrast to previous publications[43, 53] where adverse events especially of the GI tract occurred, this was not the case in our study. In fact, adverse events were overall, surprisingly, seldom. A possible reason remains the rather low dose prescribed in our clinic (mostly 1.0 mg daily) as compared to the widely reported 2 or 3mg daily in the literature.

Drugs that are used primarily as first- or second-line therapies have higher success rates compared to medications that are administered after several therapies have previously failed. Possibly this is another reason for the good efficacy seen was that colchicine was used in most cases as either primary or secondary treatment.

Even though colchicine belongs to the oldest drugs used in dermatology, there is still much to learn from it. Larger, prospective clinical trials need to be performed to receive a better insight of this high-potential drug.

Acknowledgements:

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Funding details:

There has been no funding.

Declaration of interest statement:

All authors state that they don’t have a conflict of interest.

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